Hypothalamic-Pituitary Axis

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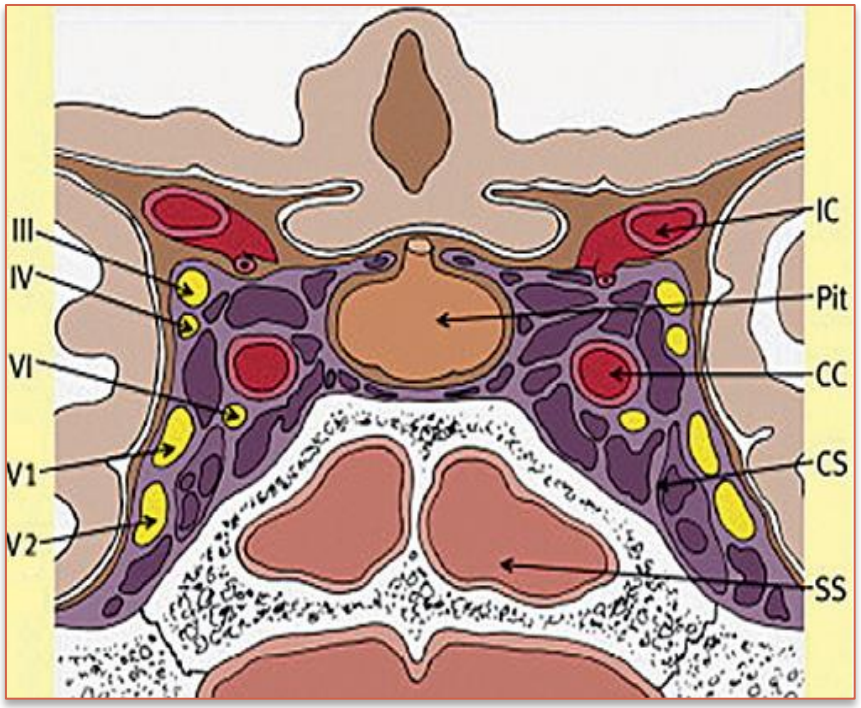
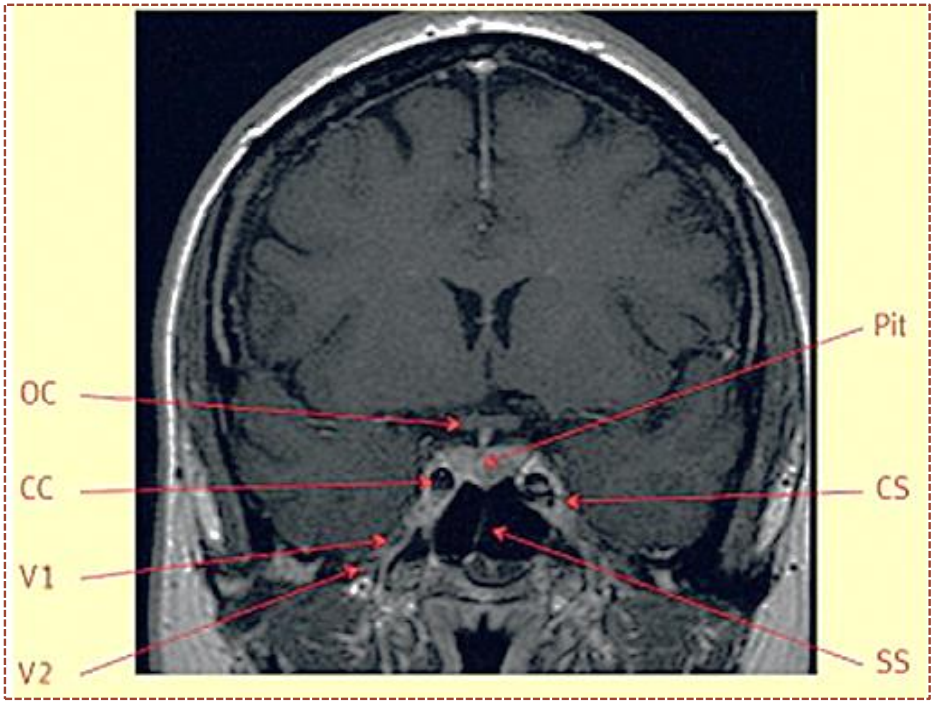
Hypothalamic-pituitary axis

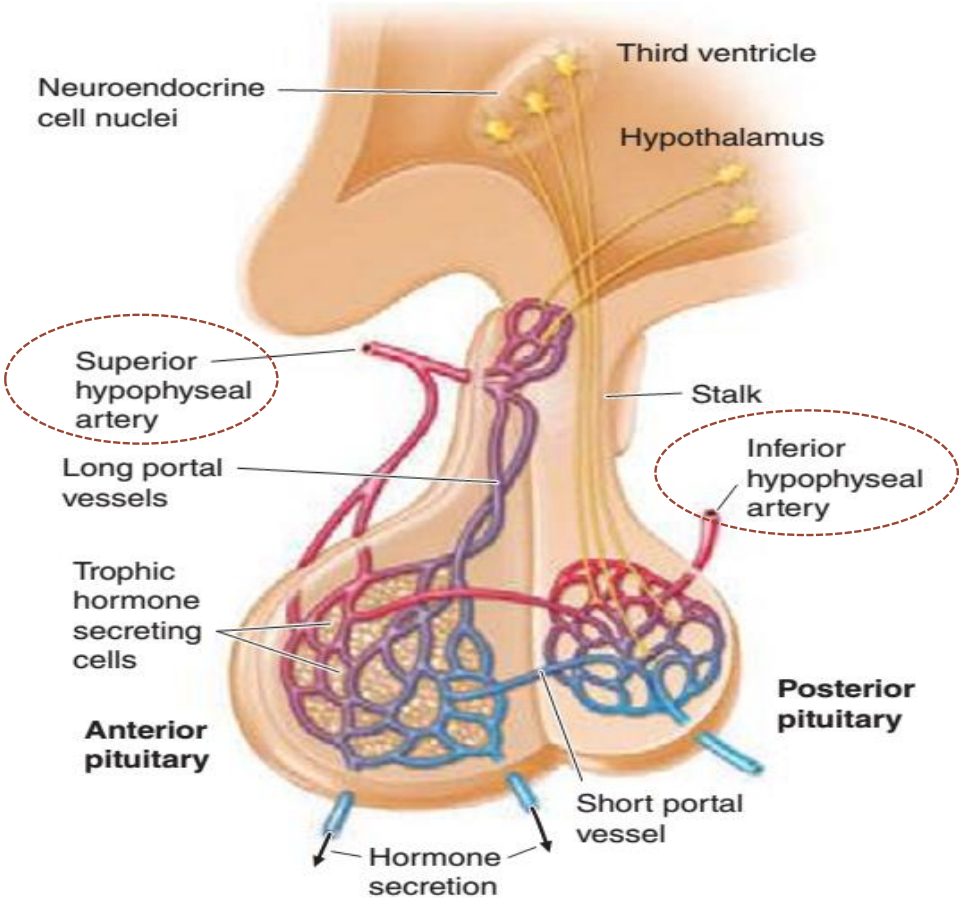




- The **pituitary gland**, weighing **500 to 900 mg**, lies at the base of the skull in the **sella turcica** within the sphenoid bone…

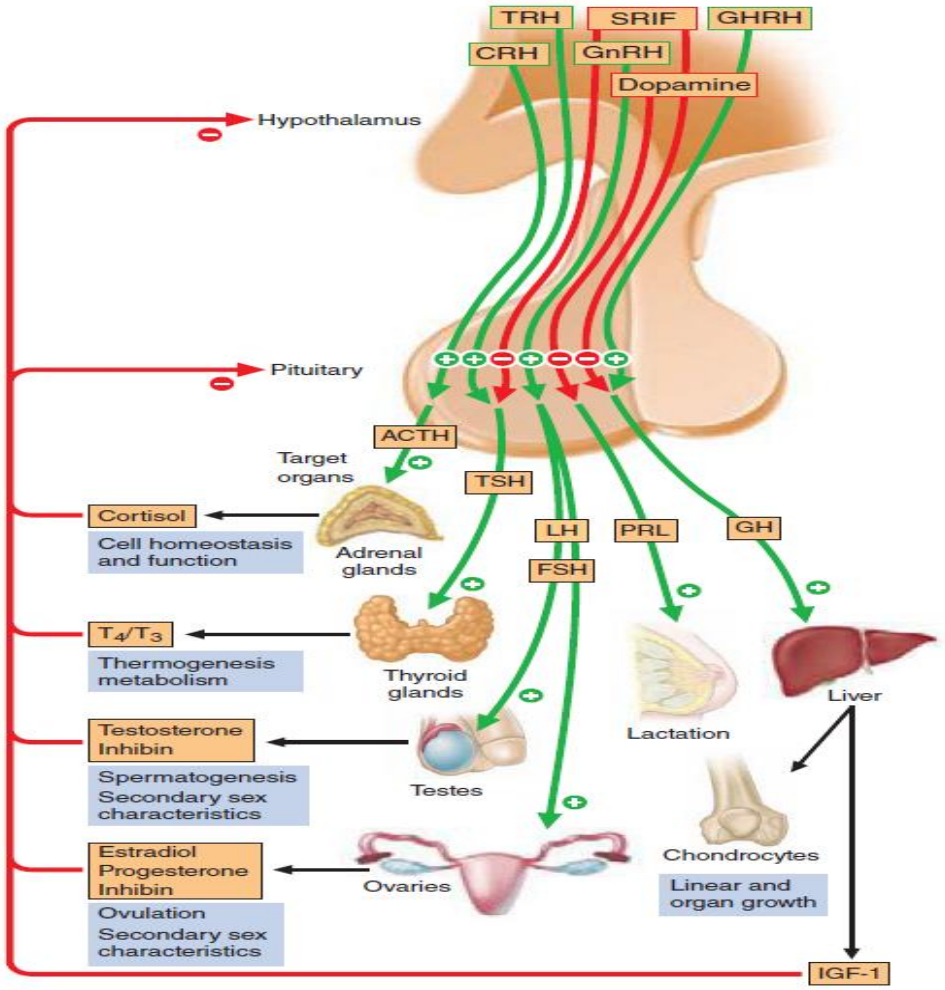
Hypothalamic-pituitary axis

- The anterior pituitary gland receives a rich vascular supply, largely from the hypothalamus via a hypothalamic-pituitary portal circulation…



Feedback control of the hypothalamic-pituitary target gland axis…

- TRH
- GNRH
- GHRH
- CRH
- SRIF
- Dopamine



Pituitary gland is composed of…

TABLE 62-1 PITUITARY–TARGET ORGAN HORMONE AXIS

HYPOTHALAMIC HORMONE	PITUITARY TARGET CELL	PITUITARY HORMONE AFFECTED	PERIPHERAL TARGET GLAND	PERIPHERAL HORMONE AFFECTED
STIMULATORY				
Anterior Lobe of Pituitary Gland				
Thyrotropin-releasing hormone (TRH)	Thyrotroph	Thyroid-stimulating hormone (TSH)	Thyroid gland	Thyroxine (T_4) Triiodothyronine (T_3)
Growth hormone-releasing hormone (GHRH)	Somatotroph	Growth hormone (GH)	Liver	Insulin-like growth factor-I (IGF-I)
Gonadotropin-releasing hormone (GnRH)	Gonadotroph	Luteinizing hormone (LH)	Ovary Testis	Progesterone Testosterone
		Follicle-stimulating hormone (FSH)	Ovary Testis	Estradiol Inhibin
Corticotropin-releasing hormone	Corticotroph	Adrenocorticotrophic hormone (ACTH)	Adrenal gland	Cortisol
Posterior Lobe of Pituitary Gland				
Vasopressin (AVP) Oxytocin			Kidney Uterus Breast	
INHIBITORY				
Somatostatin	Somatotroph Thyrotroph	GH TSH	Thyroid Liver	
Dopamine	Lactotroph	Prolactin	Breast	

Hypothalamic-pituitary axis

- Pituitary hormones are secreted in a pulsatile manner, reflecting stimulation by an array of specific hypothalamic releasing factors…

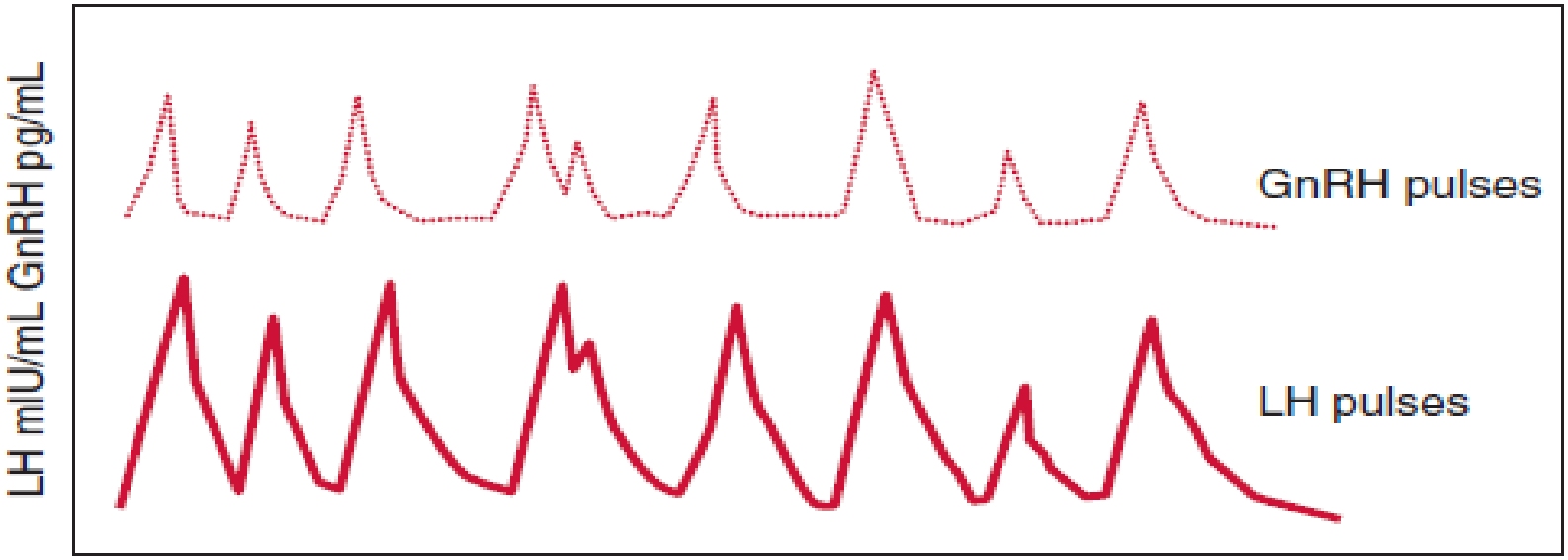


FIGURE 401e-3 Hypothalamic gonadotropin-releasing hormone (GnRH) pulses induce secretory pulses of luteinizing hormone (LH).

Pituitary Tumors

- Each of the five pituitary cell types, either singly or in combination, can give rise to benign pituitary adenomas, …
- Prolactinomas are the most common secretory pituitary tumors.
- Isolated reports of pituitary carcinomas with distant metastases have been described…

TABLE 62-2 PREVALENCE OF PITUITARY TUMORS

TUMOR	PREVALENCE (%)
Prolactinomas	40-45
Somatotroph adenomas	20
Corticotroph adenomas	10-12
Gonadotroph adenomas	15
Null cell adenomas	5-10
Thyrotroph adenomas	1-2

Pituitary Tumors

- The earliest clinical manifestations of pituitary tumors are usually the characteristic signs and symptoms caused by the hormone hyper-secretion…
- Subsequently, if the tumor is large, local manifestations of tumor enlargement may develop…
- The presence of a pituitary tumor is confirmed by pituitary MRI…
  - ✓ Microadenomas…
  - ✓ Macroadenomas…

FIGURE 403-1 **Pituitary adenoma.** Coronal T1-weighted postcontrast magnetic resonance image shows a homogeneously enhancing mass (*arrowheads*) in the sella turcica and suprasellar region compatible with a pituitary adenoma; the *small arrows* outline the carotid arteries.

Pituitary Tumors

- Compression of surrounding normal pituitary tissue by an enlarging tumor mass can cause hypo-secretion of one or several pituitary trophic hormones…

GH > LH & FSH> TSH> ACTH

- Endocrine evaluation should precede imaging studies… because 10% to 20% of the normal population harbors nonfunctional asymptomatic pituitary micro-adenomas that are incidentally detected by MRI…

Hypopituitarism

- Impaired production of one or more of the anterior pituitary trophic hormones can result from inherited disorders…
- More commonly, adult hypopituitarism is acquired and reflects:
    - Compressive mass effects of tumors
    - Local pituitary or hypothalamic traumatic
    - Inflammatory, or Vascular damage
- The clinical manifestations of hypopituitarism depend on which hormones are lost and the extent of the hormone deficiency…

TABLE 402-1 ETIOLOGY OF HYPOPITUITARISM[a]

- Development/structural
  - Transcription factor defect
  - Pituitary dysplasia/aplasia
  - Congenital central nervous system mass, encephalocele
  - Primary empty sella
  - Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, Kallmann syndrome)
- Traumatic
  - Surgical resection
  - Radiation damage
  - Head injuries
- Neoplastic
  - Pituitary adenoma
  - Parasellar mass (germinoma, ependymoma, glioma)
  - Rathke's cyst
  - Craniopharyngioma
  - Hypothalamic hamartoma, gangliocytoma
  - Pituitary metastases (breast, lung, colon carcinoma)
  - Lymphoma and leukemia
  - Meningioma
- Infiltrative/inflammatory
  - Lymphocytic hypophysitis
  - Hemochromatosis
  - Sarcoidosis
  - Histiocytosis X
  - Granulomatous hypophysitis
  - Transcription factor antibodies
- Vascular
  - Pituitary apoplexy
  - Pregnancy-related (infarction with diabetes; postpartum necrosis)
  - Sickle cell disease
  - Arteritis
- Infections
  - Fungal (histoplasmosis)
  - Parasitic (toxoplasmosis)
  - Tuberculosis
  - *Pneumocystis carinii*

Screening Tests for Pituitary Disorders

Pituitary Tumor	
Acromegaly	IGF-I OGTT: Measure BS and GH (0, 60, 120 min)
Prolactinoma	Basal serum prolactin
ACTH-secreting tumor	24-hr urine-free cortisol and creatinine level 1 mg overnight dexamethasone suppression test 2 mg and 8 mg dexamethasone suppression tests Serum ACTH Dexamethasone-CRH test Bilateral inferior petrosal sinus sampling
TSH-secreting tumor	Serum TSH, TFT
Gonadotropin-secreting tumor	FSH, LH, α subunit

Hypopituitarism	
Growth hormone deficiency	IGF-I GH provocative test: ITT Arginine-GHRH
Gonadotropin deficiency	Women: basal estradiol, LH, FSH Men: testosterone (total; free), LH, FSH
TSH Deficiency	Serum TSH, free T_4
ACTH Deficiency	ACTH Provocative test: ITT Metyrapone test Cortrosyn-stimulation test (1 mcg and 250 mcg)

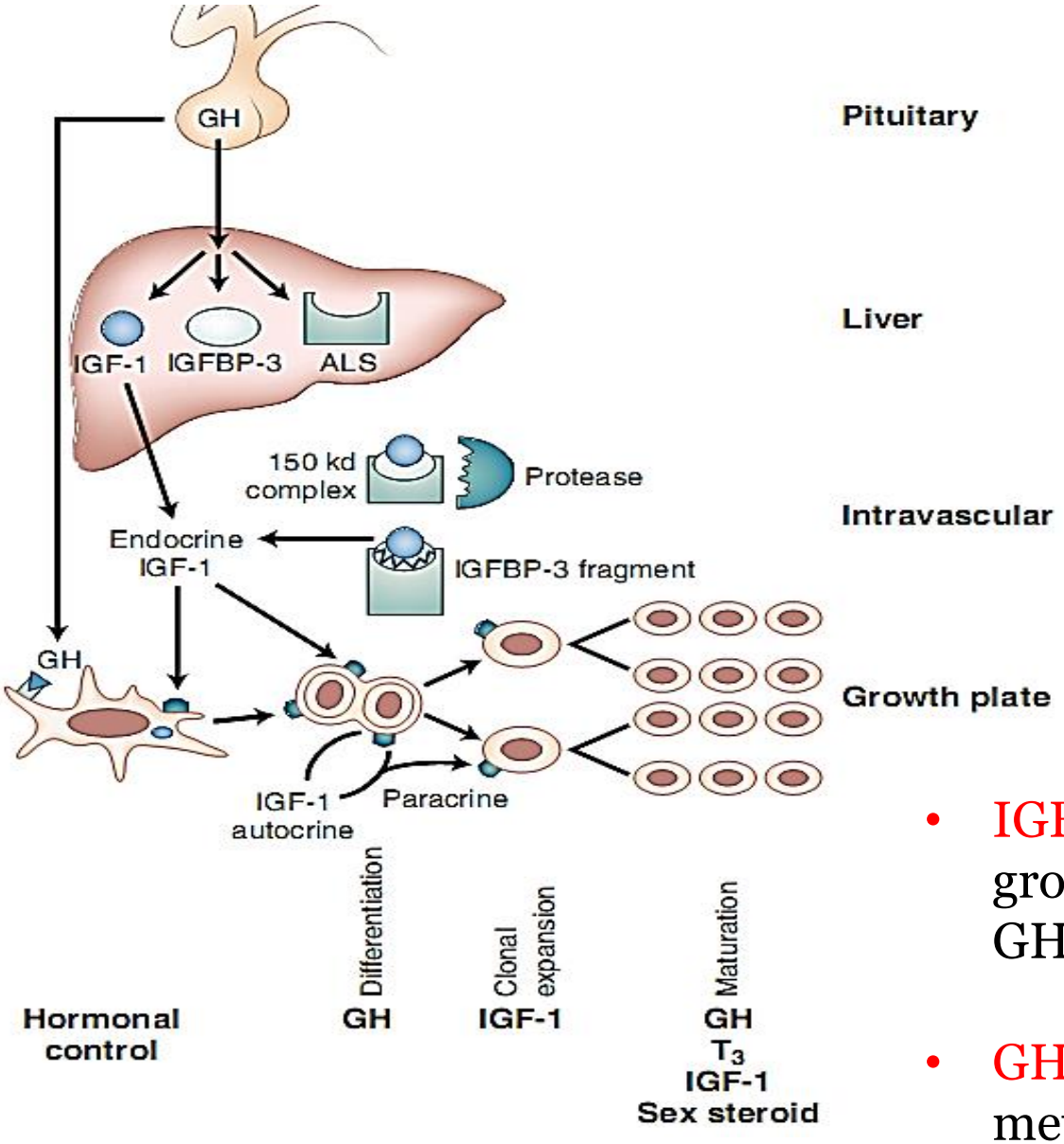
Treatment

- Dopamine agonists are choice for prolactinomas…
- For acromegaly, somatostatin analogues and GH receptor antagonists are indicated…
- For TSH-secreting tumors, somatostatin analogues and occasionally dopamine agonists are indicated…
- ACTH-secreting tumors and nonfunctioning tumors are generally not responsive to medications and require surgery and/or irradiation…

Disorders of Anterior Pituitary Hormones

GROWTH HORMONE

- A 191–amino acid peptide…
- Somatotrope cells constitute up to 50% of the total…
  - GHRH…
  - Ghrelin (induce GHRH and also directly stimulate GH release…)
  - SOMATOSTATIN (somatotropin-release inhibiting factor)
- GH binds to receptors in the liver and induces secretion of IGF-I, which circulates in the blood bound to binding proteins (IGF-BP3)…



- IGF-I mediates most of the growth-promoting effects of GH and…
- GH also affects carbohydrate metabolism…

GH deficiency during infancy and childhood

- Isolated GH deficiency is characterized by:
  - ✓ hypoglycemia due to relatively unopposed insulin action…
  - ✓ micropenis
  - ✓ short stature
  - ✓ increased fat
  - ✓ high-pitched voice
- Short stature should be evaluated if a patient's height is > 3 standard deviations (SD) below the mean for age or if the growth rate has decelerated…

LABORATORY INVESTIGATION

- Because GH secretion is pulsatile, GH deficiency is best assessed by examining the response to provocative stimuli…
  - ✓ Exercise,
  - ✓ Insulin-induced hypoglycemia,
  - ✓ Other pharmacologic tests…
- Adequate adrenal and thyroid hormone replacement should be assured before testing…
- Pituitary MRI may …

- Low serum IGF-I level is suggestive of GHD; however, a normal IGF-I level does not rule out GHD…
- A single GH stimulation test is sufficient for the diagnosis of adult GHD…
- Patients with a low serum IGF-I level and three or more pituitary hormone deficiencies have more than a 97% chance of having GHD and do not need to undergo GH stimulation testing…

TREATMENT

- Replacement therapy with recombinant GH restores growth velocity in GH-deficient children to ~10 cm/year…
- In patients with GH insensitivity and growth retardation due to mutations of the GH receptor, treatment with IGF-I bypasses the dysfunctional GH receptor…
- Patients previously diagnosed with childhood-onset GH deficiency should be re-tested as adults to affirm the diagnosis…

Features of Adult Growth Hormone Deficiency

Clinical

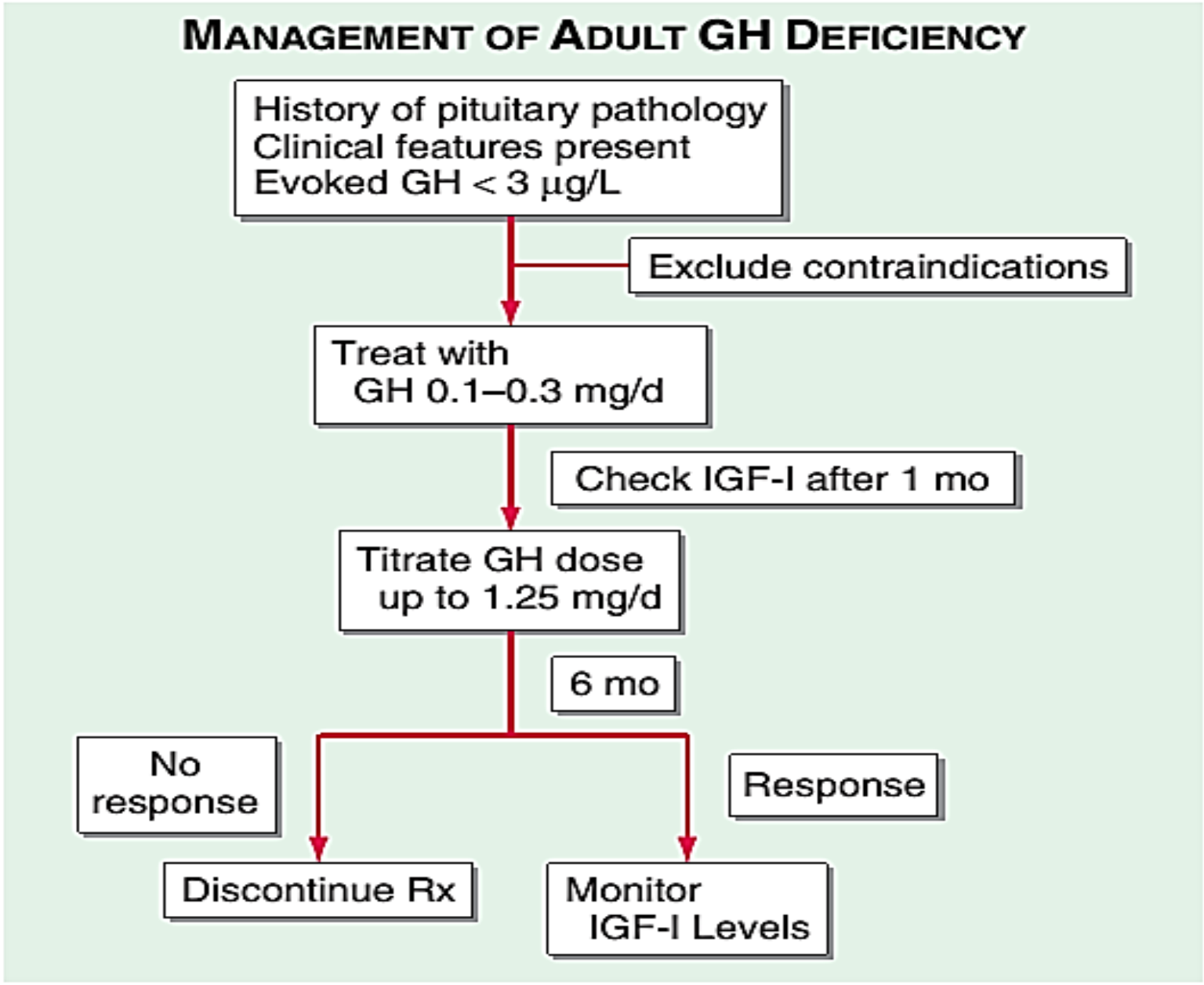
- Impaired quality of life
  - Decreased energy and drive
  - Poor concentration
  - Low self-esteem
  - Social isolation
- Body composition changes
  - Increased body fat mass
  - Central fat deposition
  - Increased waist-to-hip ratio
  - Decreased lean body mass
- Reduced exercise capacity
  - Reduced maximum O_2uptake
  - Impaired cardiac function
  - Reduced muscle mass
- Cardiovascular risk factors
  - Impaired cardiac structure and function
  - Abnormal lipid profile
  - Decreased fibrinolytic activity
  - Atherosclerosis
  - Omental obesity

Imaging

- Pituitary: mass or structural damage
- Bone: reduced bone mineral density
- Abdomen: excess omental adiposity

Laboratory

- Evoked GH <3 ng/mL
- IGF-I and IGFBP3 low or normal
- Increased LDL cholesterol
- Concomitant gonadotropin, TSH, and/or ACTH reserve deficits may be present


MANAGEMENT OF ADULT GH DEFICIENCY
History of pituitary pathology
Clinical features present
Evoked GH < 3 μg/L
Exclude contraindications
Treat with
GH 0.1–0.3 mg/d
Check IGF-I after 1 mo
Titrate GH dose
up to 1.25 mg/d
6 mo
No
response
Response
Discontinue Rx
Monitor
IGF-I Levels

Acromegaly and Gigantism…

- In childhood, GH hypersecretion leads to gigantism; In adults whose long bone epiphyses are fused, GH excess causes acromegaly…

✓ GH hypersecretion is almost always caused by a GH secreting pituitary adenoma and about 70% of patients with acromegaly have macro-adenomas…

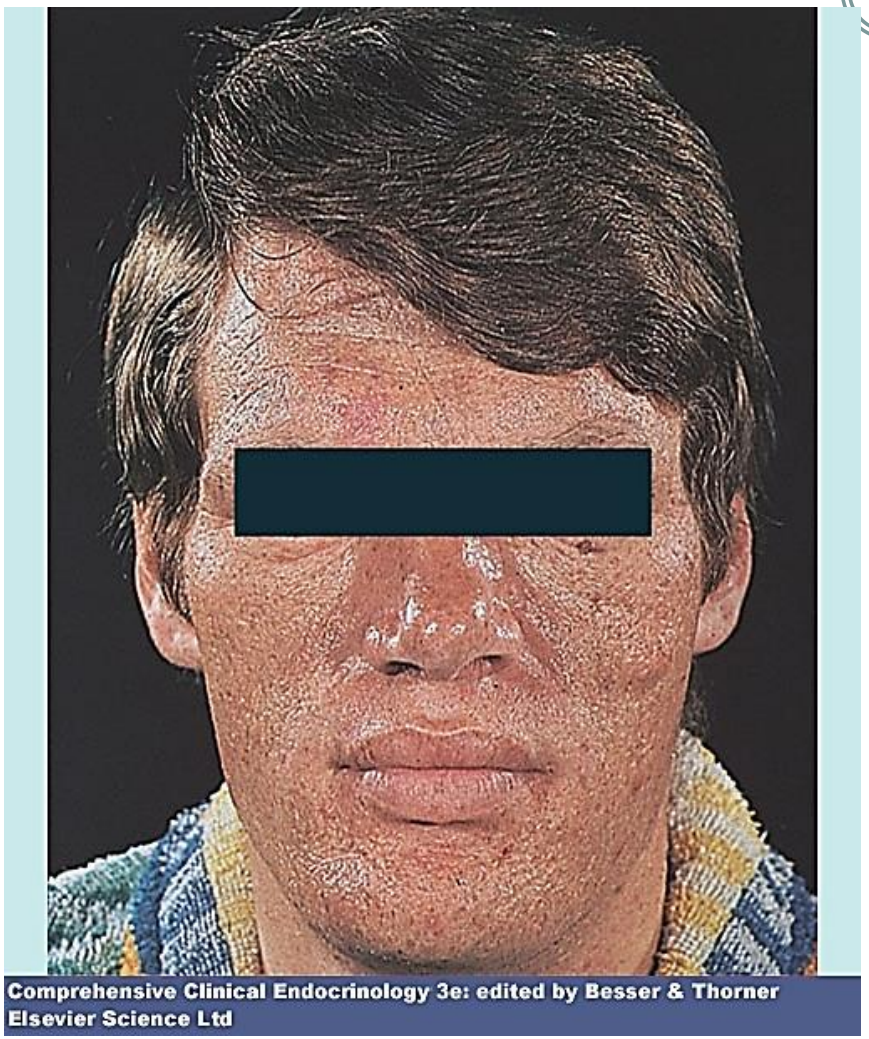
✓ Ectopic GHRH secretion can occur with pancreatic islet cell tumors and bronchial or intestinal carcinoids…

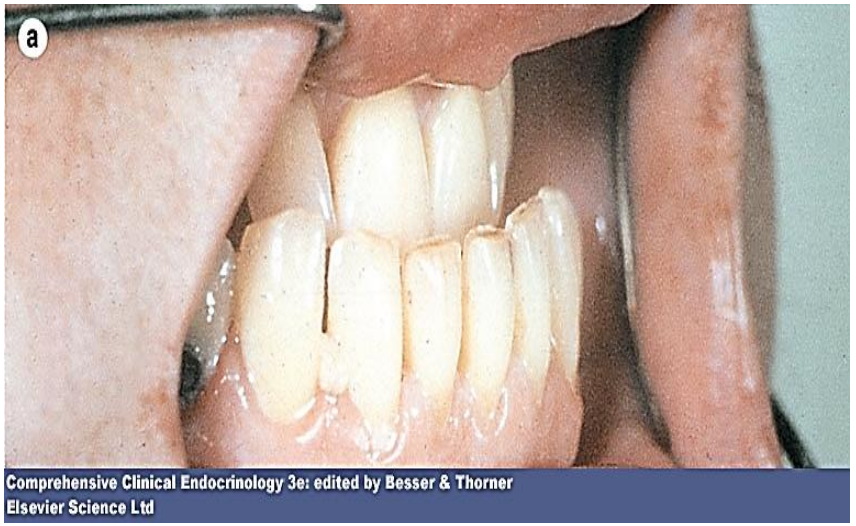
✓ Both ectopic GH and GHRH are clinically exhibited with acromegaly but are extremely rare.

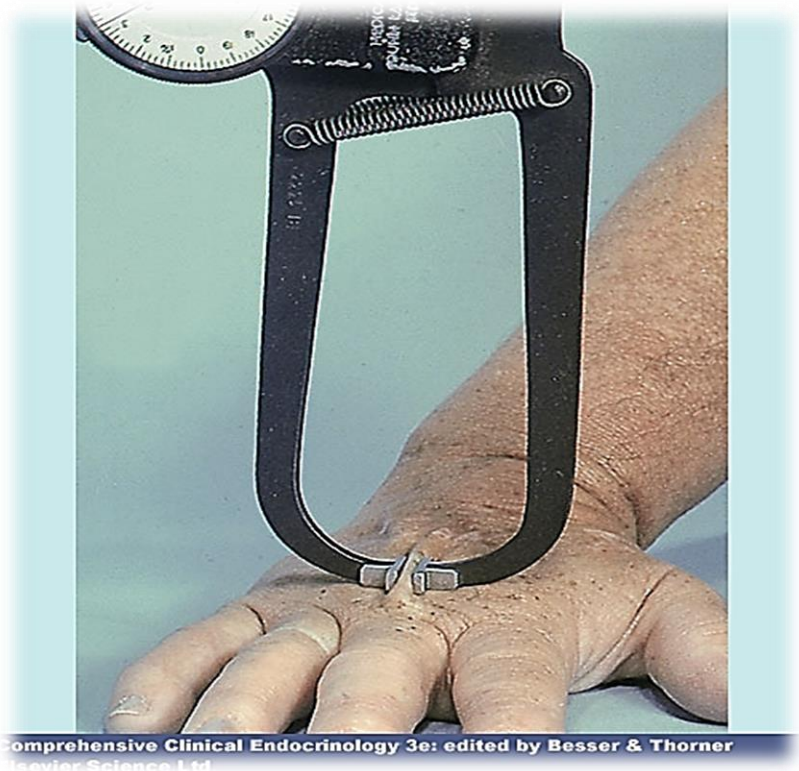
Table 65-3 Clinical Features of Acromegaly

Change	Manifestations
Somatic Changes	
Acral changes	Enlarged hands and feet
Musculoskeletal changes	Arthralgias Prognathism Malocclusion Carpal tunnel syndrome Proximal myopathy
Skin changes	Sweating
Colon changes	Polyps Carcinoma
Cardiovascular symptoms	Cardiomegaly Hypertension
Visceromegaly	Tongue Thyroid Liver
Endocrine-Metabolic Changes	
Reproduction	Menstrual abnormalities Galactorrhea Decreased libido
Carbohydrate metabolism	Impaired glucose tolerance Diabetes mellitus
Lipids	Hypertriglyceridemia

Clinical Features…






Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner
Elsevier Science Ltd


A
B
C
D

Complications…

Cardiovascular

- Ischemic heart disease
- Cardio-myopathy
- Congestive heart failure
- Arrhythmias
- Hypertension

Respiratory

- Kyphosis
- Obstructive sleep apnea

Neurologic

- Carpal Tunnel syndrome
- Stroke

Neoplastic

- Colorectal (Breast and prostate - uncertain)

Musculoskeletal

- Degenerative arthropathy , Calcific discopathy, pyrophosphate arthropathy…

Metabolic

- Diabetes mellitus/IGT and Hyperlipidemia

Causes of Death :

I-Cardiovascular (38 -62 percent)

II-Malignancy (9 -25 percent)

III-Respiratory (0 -25 percent)

Diagnosis of Acromegaly

- Random GH – not useful
- Measurement of serum IGF-I …
- Dynamic GH testing is more valuable than the measurement of a single random GH level.
- Simple and specific dynamic test for GH hypersecretion is the administration of 75 gr oral glucose (OGTT) …
- If no pituitary mass is detected, an extra-pituitary source of ectopic GH or GHRH should be sought through imaging studies of the chest and abdomen…

Treatment

- ✓ Trans sphenoidal microsurgery (TSS) is the initial therapy of choice, resulting in rapid reduction of GH levels with a low rate of surgical morbidity…
- ✓ Cure rates are proportional to preoperative tumor size with a 90% success rate for patients with micro-adenomas…

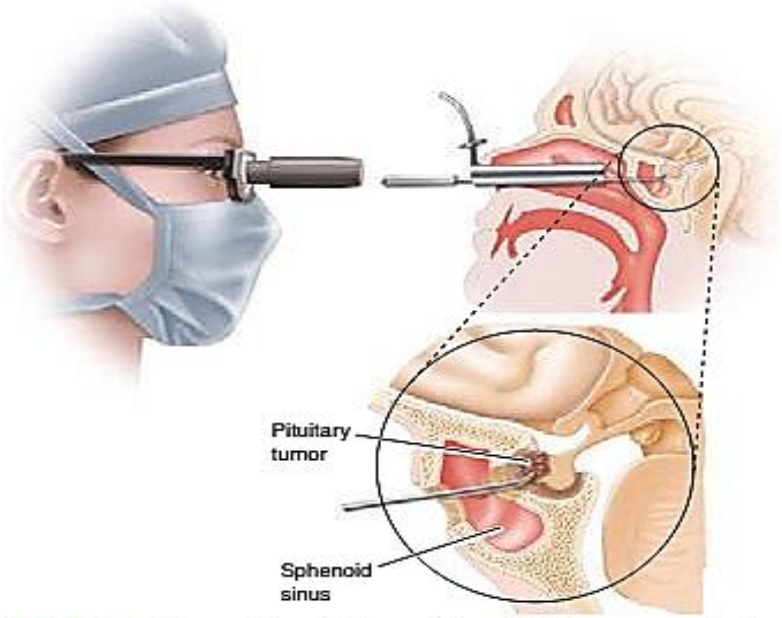


FIGURE 403-2 **Transsphenoidal resection of pituitary mass via the endonasal approach.** *(Adapted from R Fahlbusch: Endocrinol Metab Clin 21:669, 1992.)*

Medical management

- Octreotide acetate, a long-acting somatostatin analogue, is effective in reducing GH and IGF-I levels to normal in 40% to 65% of patients and shrinks tumor mass in about 50% of cases…

- A long-acting, slow-releasing depot preparation of octreotide administered once monthly is as effective as short-acting subcutaneous octreotide preparations…

- Side effects of octreotide include diarrhea, abdominal cramps, flatulence, and gallstone formation…

- Dopamine agonists, is effective in suppressing GH in only a minority of patients with acromegaly …

- The GH receptor antagonist, pegvisomant, binds to the GH receptor and normalizes IGF-1 levels in 97% of patients with acromegaly.

- Liver function tests and pituitary adenoma size must be monitored on a long-term basis…

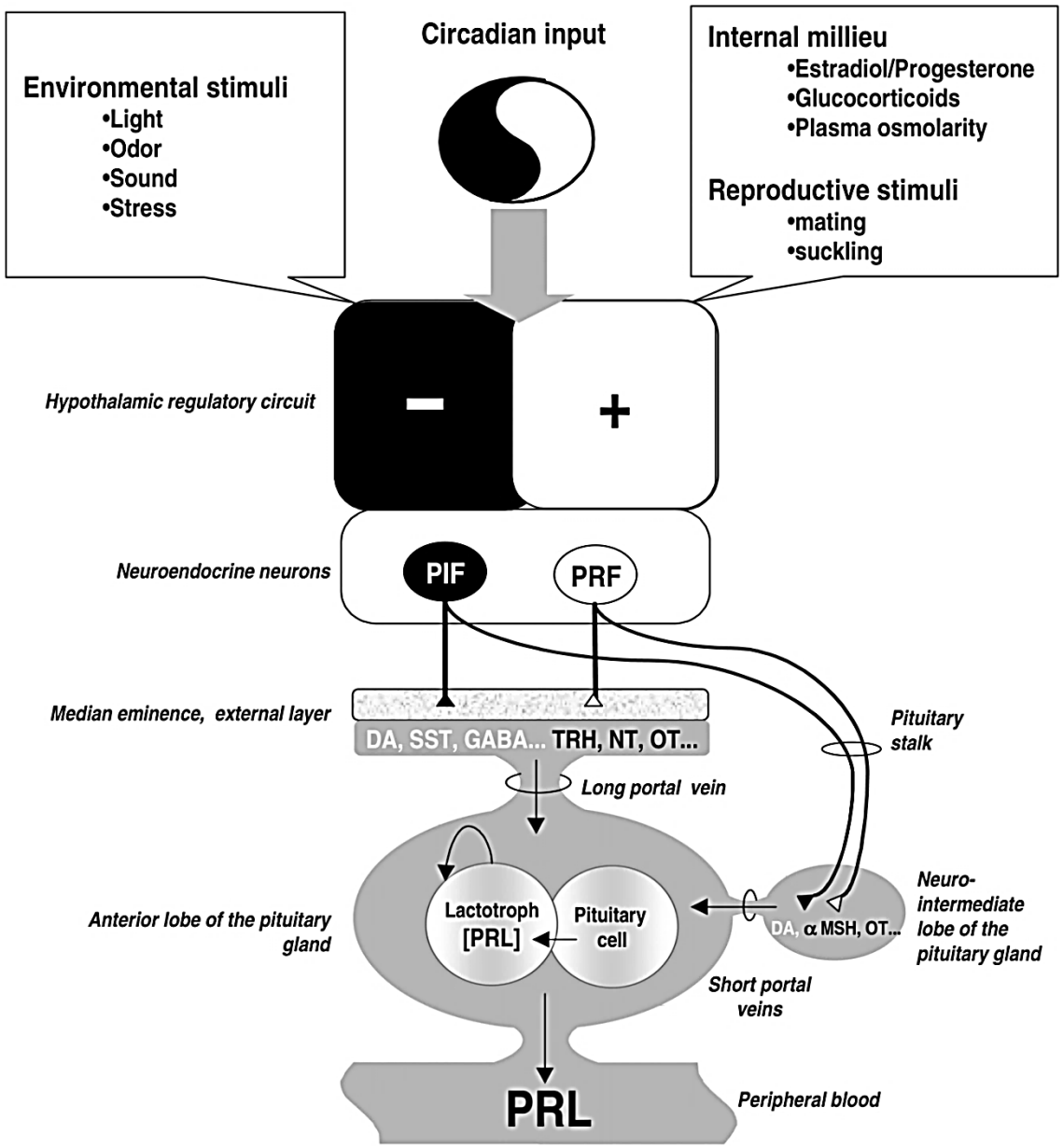
Radiotherapy

- Radiotherapy is an effective method of reducing GH hypersecretion; however…
  - It may take as long as 20 years for GH levels to fall after radiotherapy…
  - The incidence of hypopituitarism is high…

Prolactin

- With 198 amino acids and molecular mass of 21,500 kDa.
- It is weakly homologous to GH and h- placental lactogen, reflecting the duplication and divergence of a common GH-PRL-hPL precursor gene…
- PRL is synthesized in lactotropes, which constitute about 20% of anterior pituitary cells.
- PRL is unique among the pituitary hormones in that the predominant central control mechanism is inhibitory, ….
- TRH is a hypothalamic tri-peptide that elicits PRL release…

- PRL secretion is pulsatile, with the highest secretory peaks occurring during rapid eye movement (REM) sleep.
- Peak serum PRL levels (up to 30 μg/L) occur between 4:00 and 6:00 a.m. and the circulating half-life of PRL is about 50 min…
- Normal adult serum PRL levels are about 10–25 μg/L in women and 10–20 μg/L in men.



- Vasoactive intestinal peptide (VIP) also induces PRL release, whereas glucocorticoids and thyroid hormone weakly suppress PRL secretion....

Actions

- The PRL receptor is a member of the type I cytokine receptor family that also includes GH and IL-6 receptors…
- PRL acts to:
  - induce and maintain lactation,
  - decrease reproductive function, and
  - suppress sexual drive…
- PRL inhibits reproductive function by:
  - ✓ suppressing GnRH and pituitary gonadotropin secretion
  - ✓ impairing gonadal steroidogenesis in both sexes…

- In the ovary, PRL blocks folliculogenesis and inhibits granulosa cell aromatase activity, leading to:
  - anovulation
  - hypoestrogenism
- PRL also has a luteolytic effect, generating a shortened, or inadequate, luteal phase of the menstrual cycle…
- In men with hyperprolactinemia, attenuated LH secretion leads to:
  - low testosterone levels (decreased libido)
  - decreased spermatogenesis (reduced fertility)

Hyperprolactinemia

- Hyperprolactinemia is the most common pituitary hormone hyper-secretion syndrome in both men and women…
- PRL levels increase markedly (about ten-fold) during pregnancy and decline rapidly within 2 weeks of parturition.
- Serum PRL levels rise transiently after exercise, meals, sexual intercourse, minor surgical procedures, general anesthesia, chest wall injury, acute myocardial infarction, and other forms of acute stress…

Etiology Of…

I. **Physiologic hypersecretion**
   - Pregnancy
   - Lactation
   - Chest wall stimulation
   - Sleep
   - Stress

II. **Hypothalamic–pituitary stalk damage**
   - Tumors
     - Craniopharyngioma
     - Suprasellar pituitary mass
     - Meningioma
     - Dysgerminoma
     - Metastases
   - Empty sella
   - Lymphocytic hypophysitis
   - Adenoma with stalk
   - Compression
   - Granulomas
   - Rathke's cyst
   - Irradiation
   - Trauma
     - Pituitary stalk section
     - Suprasellar surgery

III. **Pituitary hypersecretion**
   - Prolactinoma
   - Acromegaly

IV. **Systemic disorders**
   - Chronic renal failure
   - Hypothyroidism
   - Cirrhosis
   - Pseudocyesis
   - Epileptic seizures

- PRL-secreting pituitary adenomas (prolactinomas) are the most common cause of PRL levels >200 µg/L…

V. Drug-induced hypersecretion

- Dopamine receptor blockers
  - Atypical antipsychotics: risperidone
  - Phenothiazines: chlorpromazine, perphenazine
  - Butyrophenones: haloperidol
  - Thioxanthenes
  - Metoclopramide
- Dopamine synthesis inhibitors
  - α-Methyldopa
- Catecholamine depletors
  - Reserpine
- Opiates
- H_2 antagonists
  - Cimetidine, ranitidine
- Imipramines
  - Amitriptyline, amoxapine
- Serotonin reuptake inhibitors
  - Fluoxetine
- Calcium channel blockers
  - Verapamil
  - Estrogens
  - Thyrotropin-releasing hormone

Etiology Of…

- Lesions of the hypothalamic-pituitary region that disrupt hypothalamic dopamine synthesis, portal vessel delivery, or lactotrope responses… are caused elevated PRL levels, usually in the range of 30–100 μg/L.

REMEMBER

Not all hyperprolactinemia is due to a prolactinoma…

- Macro-adenomas are >1 cm in diameter and may be locally invasive and impinge on adjacent structures….
- The female-to-male ratio for micro-prolactinomas is 20:1, whereas the sex ratio is near 1:1 for macro-adenomas.
- Men tend to present with larger tumors than women, possibly because the features of male hypogonadism are less readily evident…
- About 5% of micro-adenomas progress in the long term to macro-adenomas…
- Tumor size generally correlates with PRL concentrations; (values >250 µg/L usually are associated with macro-adenomas).

- Mixed tumors that secrete combinations of GH and PRL, ACTH and PRL, and rarely TSH and PRL are also seen.

- These pluri-hormonal tumors are usually recognized by immunohistochemistry (IHC), sometimes without apparent clinical manifestations from the production of additional hormones…

Presentation and Diagnosis

- Hallmarks of hyperprolactinemia in women:
  - ✓ Amenorrhea,
  - ✓ Galactorrhea (up to 80% of hyperprolactinemic women)
  - ✓ Infertility…
- If it's sustained, vertebral bone mineral density can be reduced compared with age-matched controls…
- Patients also may complain of decreased libido, weight gain, and mild hirsutism…

Presentation and Diagnosis

- In men, diminished libido, infertility, and visual loss are the usual presenting symptoms…
- In men, true galactorrhea is uncommon.
- If the disorder is long-standing, secondary effects of hypogonadism are evident, including osteopenia, reduced muscle mass, and decreased beard growth…
- In both sexes, tumor mass effects may cause visual-field defects or headache…

Laboratory Investigation

- ✓ Basal, fasting morning PRL levels…
- ✓ In females, pregnancy must always be ruled out…
- ✓ Obtain detailed drug history- rule out medication effects…
- ✓ Hypothyroidism should be excluded…

Consider MRI…, especially if high prolactin levels (> 100 ng/mL)

Treatment

- Dopamine agonists suppress PRL secretion and synthesis as well as lactotrope cell proliferation…

- About 20% of patients (especially males) are resistant to dopaminergic treatment because of these adenomas:

  1) Decreased D2 dopamine receptor numbers

  2) Post-receptor defect…

- D2 receptor gene mutations in the pituitary have not been reported.

- **Bromocriptine**

  - Starting low dose at 1.25- 2.5 mg/day at night before increasing to 2.5 – 10 mg per day in divided doses.

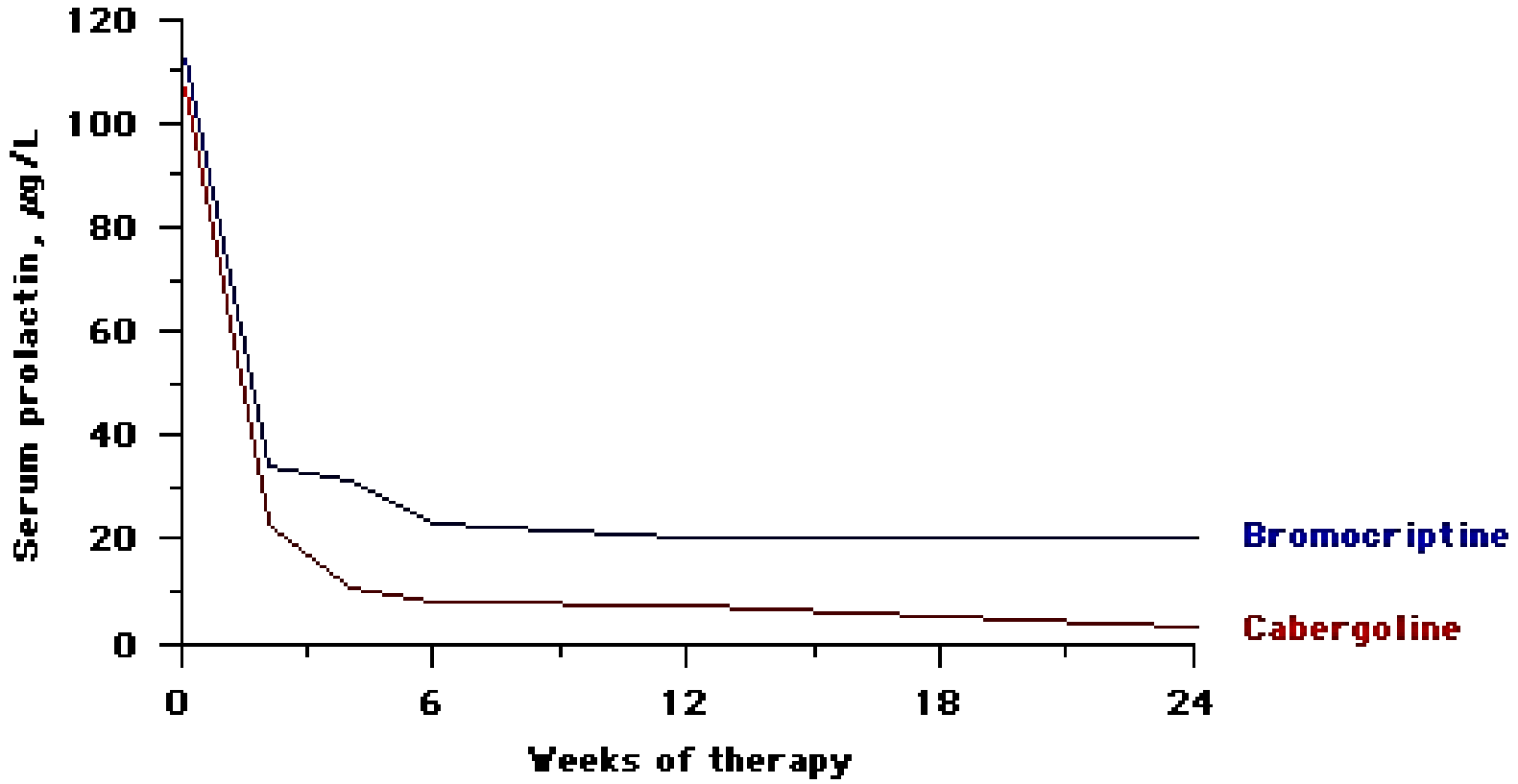
- **Cabergoline**

  - Starting (0.5–1.0 mg twice weekly) achieves normo-prolactinemia and resumption of normal gonadal function in ~80% of patients with micro-adenomas…

  - Galactorrhea improves or resolves in 90% of patients…

  - Cabergoline normalizes PRL and shrinks ~70% of macro-prolactinomas.

- Adverse effects and drug intolerance of cabergoline are encountered less commonly than with bromocriptine and also may be effective in patients resistant to bromocriptine…



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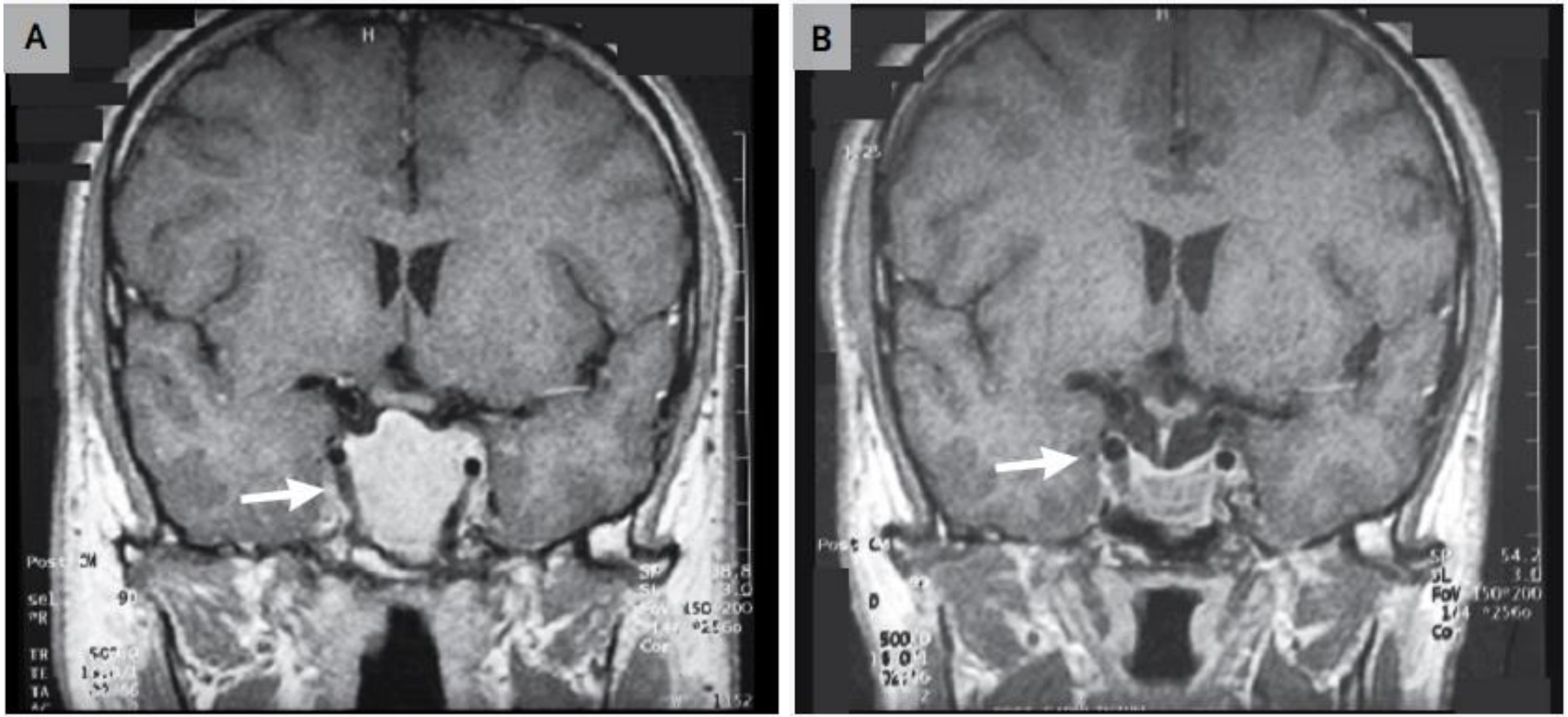
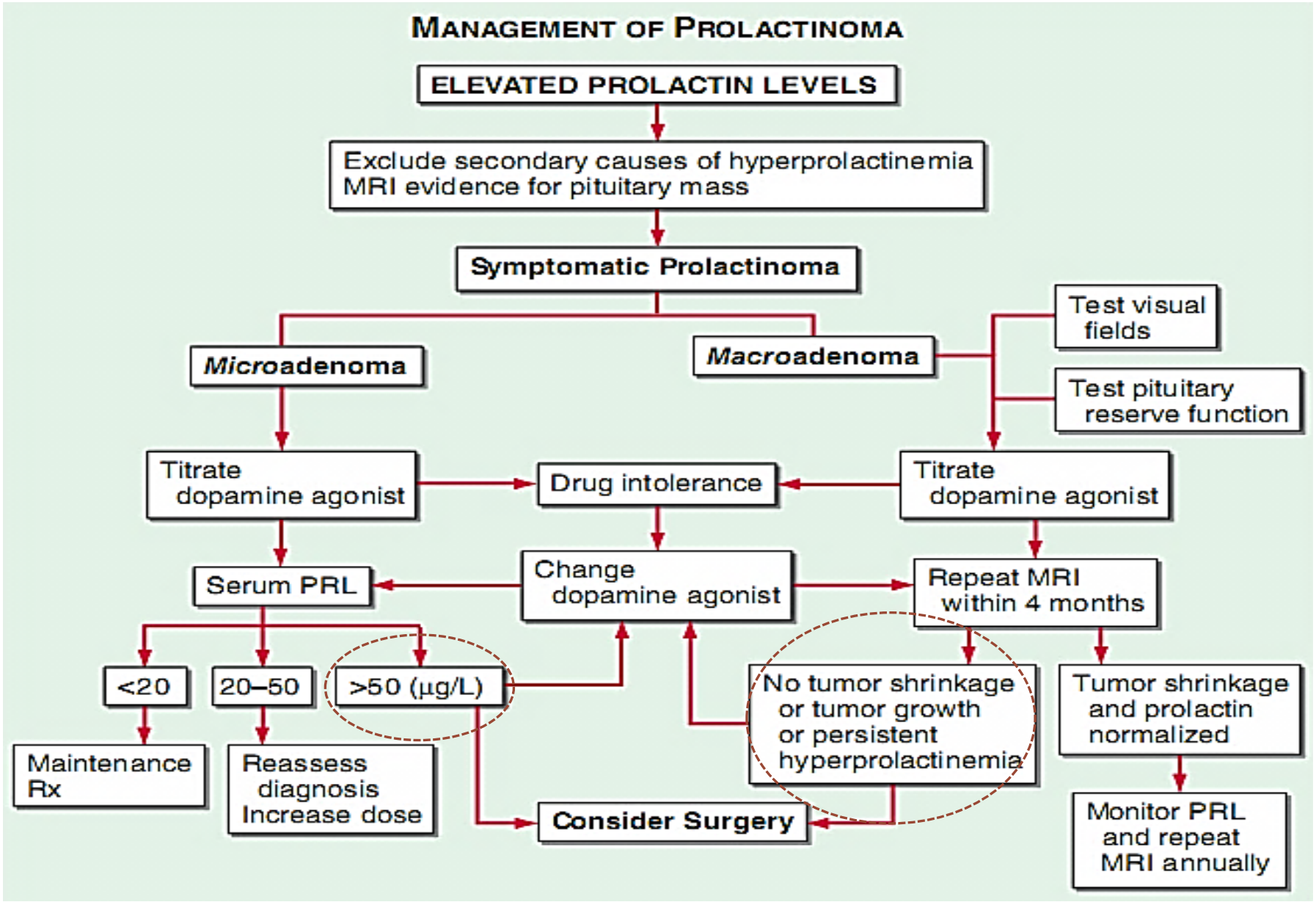


- MRI Scans Showing Tumor Shrinkage after Treatment with a Dopamine Agonist in a Patient with a Macroprolactinoma…

Surgery &…

- Indications for surgical adenoma debulking include:
  - Dopamine resistance or intolerance
  - Invasive macro-adenoma with compromised vision (that fails to improve after drug treatment)
- Initial PRL normalization is achieved in about 70% of microprolactinomas after surgical resection and only 30% of macroadenomas can be resected successfully…
- Radiotherapy for prolactinomas is reserved for patients with aggressive tumors that do not respond to maximally tolerated dopamine agonists and/or surgery.


MANAGEMENT OF PROLACTINOMA
ELEVATED PROLACTIN LEVELS
Exclude secondary causes of hyperprolactinemia
MRI evidence for pituitary mass
Symptomatic Prolactinoma
Microadenoma
Macroadenoma
Test visual fields
Test pituitary reserve function
Titrate dopamine agonist
Drug intolerance
Titrate dopamine agonist
Serum PRL
Change dopamine agonist
Repeat MRI within 4 months
<20
20–50
>50 (µg/L)
No tumor shrinkage or tumor growth or persistent hyperprolactinemia
Tumor shrinkage and prolactin normalized
Maintenance Rx
Reassess diagnosis Increase dose
Consider Surgery
Monitor PRL and repeat MRI annually


Thanks For Your
Attention

TABLE 402-2 TESTS OF PITUITARY SUFFICIENCY

Hormone	Test	Blood Samples	Interpretation
Growth hormone (GH)	Insulin tolerance test: Regular insulin (0.05–0.15 U/kg IV)	−30, 0, 30, 60, 120 min for glucose and GH	Glucose <40 mg/dL; GH should be >3 μg/L
	GHRH test: 1 μg/kg IV	0, 15, 30, 45, 60, 120 min for GH	Normal response is GH >3 μg/L
	L-Arginine test: 30 g IV over 30 min	0, 30, 60, 120 min for GH	Normal response is GH >3 μg/L
	L-Dopa test: 500 mg PO	0, 30, 60, 120 min for GH	Normal response is GH >3 μg/L
Prolactin	TRH test: 200–500 μg IV	0, 20, and 60 min for TSH and PRL	Normal prolactin is >2 μg/L and increase >200% of baseline
ACTH	Insulin tolerance test: regular insulin (0.05–0.15 U/kg IV)	−30, 0, 30, 60, 90 min for glucose and cortisol	Glucose <40 mg/dL Cortisol should increase by >7 μg/dL or to >20 μg/dL
	CRH test: 1 μg/kg ovine CRH IV at 8 A.M.	0, 15, 30, 60, 90, 120 min for ACTH and cortisol	Basal ACTH increases 2- to 4-fold and peaks at 20–100 pg/mL Cortisol levels >20–25 μg/dL
	Metyrapone test: Metyrapone (30 mg/kg) at midnight	Plasma 11-deoxycortisol and cortisol at 8 A.M.; ACTH can also be measured	Plasma cortisol should be <4 g/dL to assure an adequate response Normal response is 11-deoxycortisol >7.5 μg/dL or ACTH >75 pg/mL
	Standard ACTH stimulation test: ACTH 1-24 (cosyntropin), 0.25 mg IM or IV	0, 30, 60 min for cortisol and aldosterone	Normal response is cortisol >21 g/dL and aldosterone response of >4 ng/dL above baseline
	Low-dose ACTH test: ACTH 1-24 (cosyntropin), 1 μg IV	0, 30, 60 min for cortisol	Cortisol should be >21 g/dL
	3-day ACTH stimulation test consists of 0.25 mg ACTH 1-24 given IV over 8 h each day		Cortisol >21 g/dL
TSH	Basal thyroid function tests: T_4, T_3, TSH	Basal measurements	Low free thyroid hormone levels in the setting of TSH levels that are not appropriately increased indicate pituitary insufficiency
	TRH test: 200–500 μg IV	0, 20, 60 min for TSH and PRL[a]	TSH should increase by >5 mU/L unless thyroid hormone levels are increased
LH, FSH	LH, FSH, testosterone, estrogen	Basal measurements	Basal LH and FSH should be increased in postmenopausal women Low testosterone levels in the setting of low LH and FSH indicate pituitary insufficiency
	GnRH test: GnRH (100 μg) IV	0, 30, 60 min for LH and FSH	In most adults, LH should increase by 10 IU/L and FSH by 2 IU/L Normal responses are variable
Multiple hormones	Combined anterior pituitary test: GHRH (1 g/kg), CRH (1 μg/kg), GnRH (100 g), TRH (200 μg) are given IV	−30, 0, 15, 30, 60, 90, 120 min for GH, ACTH, cortisol, LH, FSH, and TSH	Combined or individual releasing hormone responses must be elevated in the context of basal target gland hormone values and may not be uniformly diagnostic (see text)

[a]Evoked PRL response indicates lactotrope integrity.

- **Isolated GH deficiency** is characterized by short stature, micropenis, increased fat, high-pitched voice, and a propensity to hypoglycemia due to relatively unopposed insulin action.

- Familial modes of inheritance are seen in at least onethird of these individuals and may be autosomal dominant, recessive, or X-linked. About 10% of children with GH deficiency have mutations in the *GH-N* gene, including gene deletions and a wide range of point mutations.

- Mutations in transcription factors Pit-1 and Prop-1, which control somatotrope development, result in GH deficiency in combination with other pituitary hormone deficiencies, which may become manifest only in adulthood.

- The diagnosis of *idiopathic GH deficiency* (IGHD) should be made only after known molecular defects have been rigorously excluded.

- ***GHRH receptor mutations***

- Recessive mutations of the GHRH receptor gene in subjects with severe proportionate dwarfism are associated with low basal GH levels that cannot be stimulated by exogenous GHRH, GHRP, or insulin-induced hypoglycemia, as well as anterior pituitary hypoplasia …

- The syndrome exemplifies the importance of the GHRH receptor for somatotrope cell proliferation and hormonal responsiveness.

- ***GH insensitivity*** is caused by defects of GH receptor structure or signaling.

- Homozygous or heterozygous mutations of the GH receptor are associated with partial or complete GH insensitivity and growth failure (*Laron's syndrome*).

- The diagnosis is based on normal or high GH levels, with decreased circulating GH-binding protein (GHBP), and low IGF-I levels. Very rarely, defective IGF-I, IGF-I receptor, or IGF-I signaling defects are also encountered.

- *STAT5B* mutations result in both immunodeficiency as well as abrogated GH signaling, leading to short stature with normal or elevated GH levels and low IGF-I levels Circulating GH receptor antibodies may rarely cause peripheral GH insensitivity.

- ***Nutritional Short Stature***

- Caloric deprivation and malnutrition, uncontrolled diabetes, and chronic renal failure represent secondary causes of abrogated GH receptor function.

- These conditions also stimulate production of proinflammatory cytokines, which act to exacerbate the block of GH-mediated signal transduction.

- Children with these conditions typically exhibit features of acquired short stature with normal or elevated GH and low IGF-I levels.

- ***Psychosocial Short Stature***

- Emotional and social deprivation lead to growth retardation accompanied by delayed speech, discordant hyperphagia, and an attenuated response to administered GH.

- A nurturing environment restores growth rates.